



Clinical trial results:

Randomized, double-blind, parallel group, placebo-controlled, dose finding study in colorectal cancer patients receiving 5-FU-based chemotherapy to assess the efficacy of different doses of s.c. elsiglutide in the prevention of Chemotherapy Induced Diarrhea (CID)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-000998-39 |
| Trial protocol | DE HU CZ BG |
| Global end of trial date | 09 February 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 April 2017 |
| First version publication date | 01 April 2017 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | TIDE-13-22 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02383810 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND: 73491 |

Notes:

Sponsors

| | |
|------------------------------|-------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Helsinn Healthcare SA |
| Sponsor organisation address | Via Pian Scairolo 9, Lugano/Pazzallo, Switzerland, 6912 |
| Public contact | Salvatore Chessari, MSc PhD , Helsinn Healthcare SA, +41 91 985 21 21, Salvatore.Chessari@helsinn.com |
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Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 December 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the efficacy of 3 subcutaneous (s.c.) doses of elsiglutide vs. placebo and vs. each other in the prevention of chemotherapy-induced diarrhea (CID) in colorectal cancer patients treated with 5 fluorouracil (5-FU)-based chemotherapy (FOLinic acid, Fluorouracil, OXaliplatin [FOLFOX] or FOLinic acid, Fluorouracil, IRInotecan [FOLFIRI regimen]) with no addition of a monoclonal antibody.

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in the 59th World Medical Association Assembly, Seoul), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines .

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 23 January 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Bulgaria: 32 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | Hungary: 37 |
| Country: Number of subjects enrolled | Belarus: 31 |
| Country: Number of subjects enrolled | Ukraine: 209 |
| Country: Number of subjects enrolled | Russian Federation: 182 |
| Worldwide total number of subjects | 498 |
| EEA total number of subjects | 76 |

Notes:

Subjects enrolled per age group

| | |
|-------------------------------------------|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|------------------------------------------|-----|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 331 |
| From 65 to 84 years | 167 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 538 ^[1] |
| Number of subjects completed | 498 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|----------------------------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 18 |
| Reason: Number of subjects | Physician decision: 1 |
| Reason: Number of subjects | exclusion criteria met in the Screening period: 1 |
| Reason: Number of subjects | Randomization not within protocol visit window: 1 |
| Reason: Number of subjects | Inclusion/Exclusion criteria not met (cycle 1): 19 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Overall, 538 subjects were screened, a total of 498 subjects were randomized into the study ; 40 subjects were screen failures

Period 1

| | |
|------------------------------|----------------------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Placebo and active treatments were identical in appearance. To cover the double-blind, double-dummy design, the daily administration for each of the 4 treatment groups was of 4 vials of study treatment in total including up to 4 vials of placebo in total.

Arms

| | |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Elsiglutide 10 mg - target population |

Arm description:

Elsiglutide 10 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy

| | |
|----------------------------------------|--------------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Elsiglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 10 mg/day elsiglutide.

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Arm title | Elsiglutide 20 mg - target population |
| Arm description: Elsiglutide 20 mg once daily as s.c. injection for 4 consecutive days in patients receiving F-FU based chemotherapy. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Elsiglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 20 mg/day elsiglutide. | |

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Arm title | Elsiglutide 40 mg - target population |
| Arm description: Elsiglutide 40 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Elsiglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 40 mg/day elsiglutide. | |

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Arm title | Placebo - target population |
| Arm description: Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy. | |

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Arm title | Elsiglutide 10 mg - additional population |
| Arm description: Elsiglutide 10 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Elsiglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage | |

| | |
|------------------|-------------------------------------------|
| Arm title | Elsiglutide 20 mg - additional population |
|------------------|-------------------------------------------|

Arm description:

Elsiglutide 20 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

| | |
|----------------------------------------|--------------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Elsiglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 20 mg/day elsiglutide.

| | |
|------------------|-------------------------------------------|
| Arm title | Elsiglutide 40 mg - additional population |
|------------------|-------------------------------------------|

Arm description:

Elsiglutide 40 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

| | |
|----------------------------------------|--------------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Elsiglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 40 mg/day elsiglutide.

| | |
|------------------|---------------------------------|
| Arm title | Placebo - additional population |
|------------------|---------------------------------|

Arm description:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

| | |
|----------------------------------------|--------------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

| Number of subjects in period 1 | Elsiglutide 10 mg - target population | Elsiglutide 20 mg - target population | Elsiglutide 40 mg - target population |
|-----------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Started | 120 | 122 | 120 |
| Completed | 117 | 114 | 113 |
| Not completed | 3 | 8 | 7 |
| Adverse event, serious fatal | - | 1 | 2 |
| Consent withdrawn by subject | 2 | 3 | 3 |
| Physician decision | 1 | 1 | - |
| subject did not receive study treatment | - | 1 | - |
| Adverse event, non-fatal | - | 1 | 2 |
| Other | - | - | - |
| Lost to follow-up | - | 1 | - |

| Number of subjects in period 1 | Placebo - target population | Elsiglutide 10 mg - additional population | Elsiglutide 20 mg - additional population |
|-----------------------------------------|-----------------------------|-------------------------------------------|-------------------------------------------|
| Started | 123 | 4 | 4 |
| Completed | 112 | 4 | 3 |
| Not completed | 11 | 0 | 1 |
| Adverse event, serious fatal | 3 | - | - |
| Consent withdrawn by subject | 3 | - | - |
| Physician decision | - | - | - |
| subject did not receive study treatment | - | - | - |
| Adverse event, non-fatal | 2 | - | 1 |
| Other | 2 | - | - |
| Lost to follow-up | 1 | - | - |

| Number of subjects in period 1 | Elsiglutide 40 mg - additional population | Placebo - additional population |
|-----------------------------------------|-------------------------------------------|---------------------------------|
| Started | 3 | 2 |
| Completed | 2 | 2 |
| Not completed | 1 | 0 |
| Adverse event, serious fatal | - | - |
| Consent withdrawn by subject | - | - |
| Physician decision | - | - |
| subject did not receive study treatment | - | - |
| Adverse event, non-fatal | 1 | - |
| Other | - | - |
| Lost to follow-up | - | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|----------------------------------------------------------------|---------------|-------|--|
| Number of subjects | 498 | 498 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years median standard deviation | 61 ± 9.88 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 266 | 266 | |
| Male | 232 | 232 | |

Subject analysis sets

| | |
|----------------------------|----------------|
| Subject analysis set title | FAS Target set |
|----------------------------|----------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study medication (elsiglutide or placebo) and (at least part of) the chemotherapy regimen in Cycle 1. The FAS Target set was defined as all patients from the Target population who were eligible for the FAS.

| Reporting group values | FAS Target set | | |
|----------------------------------------------------------------|----------------|--|--|
| Number of subjects | 484 | | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years median standard deviation | 61 ± 9.93 | | |
| Gender categorical Units: Subjects | | | |
| Female | 258 | | |
| Male | 226 | | |

End points

End points reporting groups

| | |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reporting group title | Elsiglutide 10 mg - target population |
| Reporting group description: | Elsiglutide 10 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy |
| Reporting group title | Elsiglutide 20 mg - target population |
| Reporting group description: | Elsiglutide 20 mg once daily as s.c. injection for 4 consecutive days in patients receiving F-FU based chemotherapy. |
| Reporting group title | Elsiglutide 40 mg - target population |
| Reporting group description: | Elsiglutide 40 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy. |
| Reporting group title | Placebo - target population |
| Reporting group description: | Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy. |
| Reporting group title | Elsiglutide 10 mg - additional population |
| Reporting group description: | Elsiglutide 10 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody. |
| Reporting group title | Elsiglutide 20 mg - additional population |
| Reporting group description: | Elsiglutide 20 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody. |
| Reporting group title | Elsiglutide 40 mg - additional population |
| Reporting group description: | Elsiglutide 40 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody. |
| Reporting group title | Placebo - additional population |
| Reporting group description: | Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody. |
| Subject analysis set title | FAS Target set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study medication (elsiglutide or placebo) and (at least part of) the chemotherapy regimen in Cycle 1. The FAS Target set was defined as all patients from the Target population who were eligible for the FAS. |

Primary: Proportion of Patients of the Target Population Experiencing a Maximum Grade \geq 2 Diarrhea in Cycle 1 (Population: FAS Target Set)

| | |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of Patients of the Target Population Experiencing a Maximum Grade \geq 2 Diarrhea in Cycle 1 (Population: FAS Target Set) ^[1] |
| End point description: | The endpoint of primary interest for efficacy was the proportion of patients within the Target population experiencing a maximum Grade \geq 2 diarrhea in Cycle 1 (as assessed by the Investigator). For patient 8031362 who withdrew consent after 11 days in Cycle 1, Investigator assessments for the individual diarrhea events were missing. The data were imputed as Grade 0 for the primary endpoint, in line with the patient's eDiary data. Grade of diarrhea according to NCI-CTCAE v 4.03 scale. Maximum grade: Maximum of the grades |

assigned by the Investigator to the individual diarrhea events during the 14-day period.

p-value 2: Chi square test, with alpha = 0.10 (2-sided)

p-value 3 : Corrected for multiplicity according to Hommel's procedure Chi square test, with alpha = 0.10 (2 sided); this is the analysis used to test for treatment superiority

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Cycle 1 was foreseen to last 14 days.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint of primary interest for efficacy was the proportion of patients within the Target population experiencing a maximum Grade ≥ 2 diarrhea in Cycle 1 (as assessed by the Investigator).

| End point values | Elsiglutide 10 mg - target population | Elsiglutide 20 mg - target population | Elsiglutide 40 mg - target population | Placebo - target population |
|---------------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 120 | 121 ^[2] | 120 | 123 |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| With maximum Grade ≥ 2 diarrhea | 2.5 | 5 | 5.8 | 9.8 |
| With maximum Grade < 2 diarrhea | 97.5 | 95 | 94.2 | 90.2 |
| p-value2 (comparison vs. placebo) | 0.019 | 0.152 | 0.255 | 0 |
| p-value2 (comparison vs. elsiglutide 10 mg) | 0 | 0.314 | 0.196 | 0 |
| p-value2 (comparison vs. elsiglutide 20 mg) | 0 | 0 | 0.764 | 0 |
| p-value3 (comparison vs. placebo) | 0.113 | 0.455 | 0.51 | 0 |
| p-value3 (comparison vs. elsiglutide 10 mg) | 0 | 0.628 | 0.471 | 0 |
| p-value3 (comparison vs. elsiglutide 20 mg) | 0 | 0 | 0.764 | 0 |

Notes:

[2] - One subject was discontinued on the date of randomization and did not receive study treatment

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Chi square test |
|----------------------------|-----------------|

Statistical analysis description:

Overall null hypothesis: All elsiglutide dose groups had equal proportion of subjects with max Grade ≥ 2 diarrhea and this was equal to the one in the placebo group. This includes 6 individual hypotheses (i.e., 3 to compare each dose group vs. placebo and 3 to compare dose groups vs. each other). Raw p-values from Chi square tests were corrected for multiplicity according to the Hommel's procedure. Each of 6 hypotheses was then evaluated based on corrected p-value at alpha 0.10 (two-sided).

| | |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups | Elsiglutide 10 mg - target population v Elsiglutide 20 mg - target population v Elsiglutide 40 mg - target population v Placebo - target population |
| Number of subjects included in analysis | 484 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.1 ^[4] |
| Method | Chi-squared |

Notes:

[3] - The overall hypothesis system was represented by the following pool of partial hypothesis systems:
 $H_{0k}: \pi G_i = \pi G_j$ $i = 1$ to 3, and $j = 2$ to 4, and $k = 1$ to 6, and $i \neq j$
 $H_{A k}: \pi G_i \neq \pi G_j$ $i = 1$ to 3, and $j = 2$ to 4, and $k = 1$ to 6, and $i \neq j$
 where πG is the probability of absence of Grade ≥ 2 CID for the Group.

Each Ho involved 2 groups.

[4] - Overall alpha level 0.10 was maintained by correction for multiplicity according to Hommel's procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

23 Jan 2015 to 09 Feb 2016

Adverse event reporting additional description:

The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day. SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set). Adverse events are reported for Cycles 1+2.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Elsiglutide 10 mg - SAF Overall set |
|-----------------------|-------------------------------------|

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.

The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.

The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Elsiglutide 20 mg - SAF Overall set |
|-----------------------|-------------------------------------|

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.

The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.

The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Elsiglutide 40 mg - SAF overall set |
|-----------------------|-------------------------------------|

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.

The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.

The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo - SAF overall set |
|-----------------------|---------------------------|

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.

The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.

The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

| Serious adverse events | Elsiglutide 10 mg - SAF Overall set | Elsiglutide 20 mg - SAF Overall set | Elsiglutide 40 mg - SAF overall set |
|---------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 124 (1.61%) | 4 / 125 (3.20%) | 3 / 123 (2.44%) |
| number of deaths (all causes) | 1 | 1 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |

| | | | |
|-------------------------------------------------------------------|-----------------|-----------------|-----------------|
| Electrocardiogram T wave inversion subjects affected / exposed | 0 / 124 (0.00%) | 1 / 125 (0.80%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypovolaemic shock subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Thrombophlebitis superficial subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac arrest subjects affected / exposed | 0 / 124 (0.00%) | 1 / 125 (0.80%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Supraventricular tachycardia subjects affected / exposed | 1 / 124 (0.81%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Disease progression | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue inflammation | | | |
| subjects affected / exposed | 0 / 124 (0.00%) | 1 / 125 (0.80%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 124 (0.00%) | 1 / 125 (0.80%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 124 (0.81%) | 1 / 125 (0.80%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urethral | | | |
| subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 124 (0.81%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 124 (0.00%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Septic shock | | | |
| subjects affected / exposed | 1 / 124 (0.81%) | 0 / 125 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|------------------------------------------------------|---------------------------|--|--|
| Serious adverse events | Placebo - SAF overall set | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 125 (4.80%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 125 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disease progression | | | |
| subjects affected / exposed | 2 / 125 (1.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Soft tissue inflammation | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Calculus urethral | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Elsiglutide 10 mg - SAF Overall set | Elsiglutide 20 mg - SAF Overall set | Elsiglutide 40 mg - SAF overall set |
|-------------------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 71 / 124 (57.26%) | 68 / 125 (54.40%) | 73 / 123 (59.35%) |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 124 (4.84%) | 7 / 125 (5.60%) | 7 / 123 (5.69%) |
| occurrences (all) | 6 | 8 | 9 |
| Leukopenia | | | |
| subjects affected / exposed | 6 / 124 (4.84%) | 10 / 125 (8.00%) | 6 / 123 (4.88%) |
| occurrences (all) | 6 | 11 | 6 |
| Neutropenia | | | |
| subjects affected / exposed | 32 / 124 (25.81%) | 29 / 125 (23.20%) | 26 / 123 (21.14%) |
| occurrences (all) | 44 | 34 | 34 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 124 (7.26%) | 8 / 125 (6.40%) | 7 / 123 (5.69%) |
| occurrences (all) | 11 | 9 | 9 |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 124 (0.81%) | 3 / 125 (2.40%) | 10 / 123 (8.13%) |
| occurrences (all) | 3 | 4 | 33 |

| | | | |
|-----------------------------|-------------------|-------------------|-------------------|
| Gastrointestinal disorders | | | |
| Abdominal tenderness | | | |
| subjects affected / exposed | 0 / 124 (0.00%) | 11 / 125 (8.80%) | 7 / 123 (5.69%) |
| occurrences (all) | 0 | 37 | 17 |
| Nausea | | | |
| subjects affected / exposed | 21 / 124 (16.94%) | 17 / 125 (13.60%) | 15 / 123 (12.20%) |
| occurrences (all) | 27 | 23 | 23 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 124 (0.81%) | 3 / 125 (2.40%) | 7 / 123 (5.69%) |
| occurrences (all) | 2 | 3 | 8 |

| | | | |
|-------------------------------------------------------|---------------------------|--|--|
| Non-serious adverse events | Placebo - SAF overall set | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 72 / 125 (57.60%) | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 125 (7.20%) | | |
| occurrences (all) | 14 | | |
| Leukopenia | | | |
| subjects affected / exposed | 12 / 125 (9.60%) | | |
| occurrences (all) | 13 | | |
| Neutropenia | | | |
| subjects affected / exposed | 32 / 125 (25.60%) | | |
| occurrences (all) | 44 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 125 (5.60%) | | |
| occurrences (all) | 13 | | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal tenderness | | | |
| subjects affected / exposed | 7 / 125 (5.60%) | | |
| occurrences (all) | 19 | | |
| Nausea | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 17 / 125 (13.60%) | | |
| occurrences (all) | 23 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 125 (4.00%) | | |
| occurrences (all) | 5 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 02 December 2014 | <p>The protocol for this study was amended once. This amendment was implemented before the first patient was included in the study.</p> <p>Reasons for Amendment 1, dated 02 Dec 2014 were:</p> <ul style="list-style-type: none">• It was clarified that exclusion criteria 17 to 23 were to be checked on Day 1 of Cycle 1 as well as Day 1 of Cycle 2.• It was clarified that the Investigator is not kept blinded with regards to the patient's judgment about the occurrence of diarrhea.• The reporting of diarrhea events in the context of AE reporting was clarified.• It was defined that elsiglutide AEs included in the MedDRA high level term "injection site reactions" will be considered as AEs of special interest.• It was clarified that only IWRS, no Interactive Voice Response System was used in the study.• It was clarified that preventive measures against CID other than medications are permitted.• The nomenclature and use of documents was clarified for the Drug Preparation Form and the IWRS randomization confirmation e-mail.• It was clarified that urinalysis will not be restricted to dipstick analysis and that results for urine sample analysis did not have to be available for administration of study treatment on Day 1 to commence.• The description of the statistical analysis for QoL data and for vital signs data was corrected.• The Declaration of Helsinki was removed from the list of appendices and instead included in the list of references.• Administrative information and administrative changes:<ul style="list-style-type: none">- The bioanalytical laboratory for citrulline testing and the company responsible for clinical trial supplies, packaging, and labelling were mentioned.- The contact details of sponsor representatives were adapted to show the actual address instead of a post-box address.• Minor text changes were implemented to clarify information, improve readability and remove incorrect or ambiguous wording. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported